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10/722,176	11/24/2003	Tariq M. Rana	UMY-059	3047

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LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,176	RANA, TARIQ M.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 17-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 17-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/07/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/7/2006 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 11/7/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/07/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 11/7/2006, claims 14, 17-34, 38-42 and new claims 43-44 are pending in the application.

Response to Declaration

The declaration filed on 11/07/2006 under 37 CFR 1.132 has been considered but is ineffective to overcome the rejections of record.

Applicants submit the declaration shows use of a generation 4 dendrimer in the presently claimed invention as evidenced by the description of the results in a manuscript submitted after the filing date of the instant application. Applicants state the use of the generation 4 dendrimer is effective in delivering a siRNA to target cells. The declaration is ineffective to overcome the rejections of record because first, the declaration does not show priority of invention earlier than the prior art references of record and further because showing the use of a generation 4 dendrimer does not overcome the rejections of record, namely the Yoo et al. reference, as fully explained herein.

Thus, the declaration is ineffective to overcome the rejections of record.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14 and 17-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims are drawn to a delivery mixture comprising a generation 2 to 5 dendrimer, and more specifically a generation 5 dendrimer, and a nucleic acid capable of mediating RNA interference (RNAi).

Applicant points to Figures 6A-C and paragraphs 0025-0027, 0102-0103 and paragraph 0111 for support for the claim amendments however the specification and specifically Figures 6A-C and paragraphs 0025-0027, 0102-0103 and paragraph 0111 does not provide support for a "generation 2 to 5 dendrimer" nor provide support for a "generation 4 dendrimer."

Figures 6A, 6B and 6B as well as the explanation of the drawings on page 4 of the specification depict branched dendrimers and a PEG dendrimer and do not show a generation 2 to 5 dendrimer. The specification on page 12, lines 1-12 disclose the use of dendrimers to delivery a siRNA and disclose the dendrimers as "highly branched dendrimers with well-defined architecture"; however the specification does not disclose the use of generation 2 to 5 dendrimer in a delivery mixture nor does the specification specifically disclose the use of a generation 4 dendrimer. The specification in Examples 1 or 2 disclose the use of a PAMAM dendrimer in a delivery mixture comprising a siRNA; however the specification does not disclose the use of PAMAM dendrimer is a generation 2 to 5 dendrimer.

Furthermore the amendment filed 11/07/2006, adding the limitation "generation 2 to 5 dendrimer" and "generation 4 dendrimer" represents a departure from the claims as originally filed. If Applicant believes that such support is present in the specification and

claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Therefore, instant claims 14 and 17-44 are accorded a filing date of 11/24/2003.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the limitation "wherein the siRNA" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000.

Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 14, 20, 22-24 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Frecht et al. (U.S. Patent No. 7,097,856).

The instant claims are drawn to a delivery mixture comprising a generation 2 to 5 dendrimer and a nucleic acid capable of mediating RNAi wherein the nucleic acid is an RNA molecule, wherein the RNA is a siRNA, wherein dendrimer is a generation 4 dendrimer.

Frecht et al. teach making dendrimers that are useful as delivery vehicles for nucleic acids. Frecht et al. teach a specific embodiment of a generation 4 dendrimer (Figure 1 and column 3, lines 7-18) and teach preferred dendrimers are from generation 1 to generation 5 (see column 15, lines 59-68). Frecht et al. teach the use of double stranded RNA (see column 4, lines 8-33), which would meet the limitation of nucleic acids capable of mediating RNAi as the specification defines siRNA as double stranded RNA molecules (see page 7).

Thus, Frecht et al. anticipates claims 14, 20, 22-24 and 43 of the instant application.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 19-20, 23-34 and 38-42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woolf (cited on PTO Form 892 filed 08/23/05), Olejnik et al. (cited on PTO Form 892 filed 08/23/05), Grigoriev et al. (cited on PTO Form 892 filed 08/23/05) and Yoo et al. (cited on PTO Form 892 filed 08/23/05).

Woolf teach a delivery complex comprising a PAMAM complex (see paragraph 0203) and a double stranded RNA (see paragraphs 0048-0050). Woolf teach the dsRNA is between 18 and 29 nucleotides in length (see paragraph 0071) and wherein the dsRNA comprises a sense and antisense strand complementary to a target mRNA sequence (see paragraph 0176). Woolf teaches modifications comprising conjugates and detectable moieties linked to the 3' terminus of the double stranded RNA (see paragraph 0096 and 0109-0110). Woolf does not teach the dendrimers are generation 2 to 5, does not teach dsRNA comprising photocleavable biotin modifications and does not teach double stranded RNA containing psoralen crosslinks.

Yoo et al. teach a complex comprising generation 5 dendrimers and antisense oligonucleotides are efficient at delivering said oligonucleotide to cells. Yoo et al. teach the complex of dendrimer to oligonucleotide at various ratios for determination of the effective delivery of said complex.

Olejnik et al. teach oligonucleotides comprising photocleavable biotin (see page 362).

Grigoriev et al. teach incorporation of psoralens into oligonucleotide for formation of psoralen crosslinks (see Figure 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate modifications such as photocleavable biotin and crosslinks using psoralens, into the dsRNA. It would have been further obvious to one of skill in the art to use small dendrimer complexes for delivery of oligonucleotides into cells.

One would have been motivated to use small dendrimer complexes as a delivery agent for oligonucleotides because Yoo et al. demonstrates efficient delivery of small oligonucleotide/dendrimer complexes in to cells. Additionally, Yoo et al. demonstrate the routine nature of testing various ratios of dendrimer to oligonucleotide, from 15 ug/ml to 90 ug/ml (see Figure 1 and Figure 2) for optimization of the most efficient ratio for delivery and gene inhibition. One would have been further motivated to incorporate a photocleavable biotin modification into the siRNA contained in the delivery mixture comprising a dendrimer because Olejnik et al. teach incorporation of a photocleavable biotin into a oligonucleotide provides a simple method for purification of oligonucleotides (see abstract). Additionally, Olejnik et al. teach incorporation of a photocleavable biotin allows isolation of nucleic acids after synthesis and after cleavage of the biotin moiety, the functional nucleic acids can be used in further methods (see page 361). Further, one would have been motivated to incorporate psoralens, as taught by Grigoriev et al., into the siRNA contained in the delivery mixture to increase the target specificity of the siRNA to the target gene once the siRNA is delivered to cells. Grigoriev et al. teach addition of psoralen derivatives to oligonucleotides increase the antisense target affinity and half-life by crosslinking the antisense oligonucleotide to the target (see page 3501).

One would have had a reasonable expectation of success of at using a small dendrimer in a complex comprising a nucleic acid capable of mediating RNAi given that Yoo et al. demonstrated delivery of a nucleic acid in a complex comprising a generation 5 dendrimer and one would expect a nucleic acid such as a siRNA to form a complex with a dendrimer similar to a nucleic acid such as an antisense molecule. Additionally, it is a matter of routine skill in the art to use the dendrimer and oligonucleotide at different concentrations to determine the effective ratio of dendrimer to oligonucleotide for efficient delivery into cells. Further, one would have had a reasonable expectation of success at incorporating a photocleavable biotin and psoralen crosslinks into the siRNA contained in the delivery mixture because Olejnik et al. teach synthesis of an oligonucleotide comprising a photocleavable biotin and teach efficient purification of the oligonucleotide and photocleavable of the biotin moiety and further Grigoriev et al. teach efficient inhibition of gene expression using cross linked nucleic acids.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 14, 17-24 and 32-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (cited on PTO Form 892 filed 08/23/05) in view of Hammond et al. (cited on PTO Form 892 filed 08/23/05), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05).

The instant claims are drawn to a delivery mixture comprising a 2 to 5 generation dendrimer and a nucleic acid capable of mediating RNAi wherein the nucleic acid comprises an RNA precursor, wherein the nucleotide sequence that encodes an RNA precursor is operably linked to a polymerase III promoter, wherein the nucleic acid is an RNA molecule, wherein the RNA is a miRNA, a shRNA or a siRNA, wherein the siRNA comprises a sense and antisense strand complementary to a target mRNA sequence, wherein the sense and antisense strands are crosslinked, wherein the crosslink is psoralen, wherein the siRNA comprises a modification at the 3'OH terminus, wherein the modification is selected from group as listed in claim 29-30, wherein the dendrimer is PAMAM and wherein the siRNA is from 16-30, 23-32 or 21 nucleotides in length..

Yoo et al. teach a delivery mixture comprising a PAMAM dendrimer and an antisense nucleic acid capable of inhibiting gene expression (see page 1799 to 1800). Yoo et al. specifically teach a complex comprising a generation 5 dendrimer and an antisense wherein the complex displayed substantial activity for the delivery of said oligonucleotide. Yoo et al. teach various ratios of dendrimer to nucleic acid for optimization. Yoo et al. do not teach a dsRNA or a RNA precursor capable of mediating RNAi.

Hammond et al. teach two molecules used for silencing specific genes: antisense and dsRNA. Hammond et al. teach that although antisense methods are straightforward techniques for probing gene function, the methods have suffered from "...questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach ..."dsRNAs have been shown to inhibit gene expression

in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression."

Tuschl et al. teach siRNA molecules, 19-23 nucleotides in length comprising 3' nucleotide overhangs, that mediate RNAI and wherein the nucleotides of the sense strand and antisense strand are complementary to the target gene (see page 6, lines 8-15 and Figure 14).

McManus et al. teach shRNA and microRNA, which mediate RNAi (see page 740) and further teach a nucleic acid encoding a RNA precursor operably linked to a polymerase III promoter wherein the RNA precursor mediates RNAi (see figure 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the delivery mixture comprising a dendrimer for delivering a dsRNA instead of an antisense molecule.

One would have been motivated to make a delivery mixture comprising a dendrimer and a siRNA instead of an antisense because Hammond et al. teach that siRNA are more efficient than antisense for probing gene function and for inhibiting gene expression. In probing gene function and inhibition of gene expression, one of skill in the art would be motivated to use the most efficient methodology and therefore one would have been motivated to use siRNA or miRNA because Tuschl et al. and McManus et al. teach both siRNA and miRNA mediate RNAi efficiently in cells, thereby allowing elucidation of gene function. Because dsRNA is a nucleic acid, one would expect to encounter similar issues in delivery to cells as with antisense oligonucleotides and therefore one would be motivated to use a delivery mixture comprising a dendrimer

because the goal for siRNA therapy is optimal delivery of the siRNA and enhanced cellular uptake by the cells. Yoo et al. teach a delivery mixture comprising a dendrimer provides advantages such as extended circulation lifetime, formation of stable complexes with oligonucleotides and increased concentration at the target site in the presence of serum; advantages that are not see in other commercially available delivery agents (see page 1999 and last paragraph page 1803). Additionally, Yoo et al. demonstrate the routine nature of testing various ratios of dendrimer to oligonucleotide, from 15 ug/ml to 90 ug/ml (see Figure 1 and Figure 2) for optimization of the most efficient ratio for delivery and gene inhibition and therefore because the use of dendrimers in a delivery mixture, as claimed by the instant invention, were known to add benefits to delivery of oligonucleotides molecules to cells, one would have been motivated to make a delivery mixture comprising siRNA and test various ranges for the optimal concentration.

Finally, one would have a reasonable expectation of success because Yoo et al. teach antisense nucleic acids molecules can be delivered to cells using a delivery mixture comprising a dendrimer and Hammond et al. teach that of the two molecules used to administer to cells for silencing gene function, dsRNA is more potent and sequence specific than antisense. One would have a reasonable expectation of success to make a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi because Tuschl et al. and McManus et al. teach siRNA and miRNA that efficiently mediated RNAi and further one would expect the nucleic acids taught by

Yoo et al. and the nucleic acids taught by Tuschl et al. and McManus et al. to be similarly delivered using a mixture comprising a dendrimer.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicants Arguments

Claim Rejections - 35 USC § 102

The rejection of record of claims 14, 19-20, 23-24 and 33-34 under 35 U.S.C. 102(e) as being anticipated by Woolf (US 2006/0009409) is withdrawn in response to claim amendments filed 11/07/2006.

Claim Rejections - 35 USC § 103

The rejection of record of claims 14, 19-20, 23-24 and 33-34 under 35 U.S.C. 103(a) as being unpatentable over Woolf (US 2006/0009409) in view of Olejnik et al. (Nucleic Acids Research, 1996) in view of Grigoriev et al. (PNAS 1993) is withdrawn in response to claim amendments filed 11/07/2006.

The rejection of record of claims 14, 17-24, 32-34 and 38-42 under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (PTO Form 892 filed 08/23/05) in view of Hammond et al. (Nature 2001, Vol. 2: 110-119), Tuschl et al. (WO 02/44321) and McManus et al. (Nature Review: Genetics 2002) is maintained.

Applicant's arguments are acknowledged but not found persuasive. Applicant argues Yoo et al. teach complexes of antisense RNA and dendrimers wherein the dendrimers are not particles and that this "...is a direct contradiction of clear evidence it the art that such complexes formed with PA[M]AM dendrimers are particles." Therefore, Applicants position is that there is a strong factor against combining the Yoo et al. reference with the other cited references. Applicants further argue Yoo et al. teach the use of a generation 4 dendrimer that was ineffective in delivery the nucleic acid to the cells and therefore the "[f]ailure of others is one of the secondary considerations, or indicia of nonobviousness" and further there would be no reasonable expectation of success at substituting a siRNA for an antisense oligonucleotide in the complex comprising a dendrimer.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., complexes of antisense RNA and dendrimers wherein the dendrimers are *not particles*) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant's arguments that because Yoo et al. teach a generation 4 dendrimer was ineffective, the invention would not be obvious are simply not convincing. While it is correct that Yoo et al. does state "[a] generation 4 dendrimer was relatively ineffective under all circumstances" (see page 1801 column 1), the "circumstances" Yoo et al. was referring to were the serum effects on oligonucleotide delivery by dendrimers and not

the use of a dendrimer 4 as a whole as a delivery agent. Further, the instant claims are drawn to the use of generation 2 to 5 dendrimers and Yoo et al. specifically teach "generation 5 dendrimer displayed substantial activity for the delivery of oligonucleotides" and states the use of small oligonucleotide/dendrimer complexes provide many advantages for *in vivo* applications. Thus, Yoo et al. anticipates the instant invention. Applicant cites a post filing reference, Kang et al., for their position that there would have been no reasonable expectation of success at delivering a complex comprising a siRNA and a dendrimer because Kang et al. teach the complex was 'poorly effective for the delivery of siRNA." One of skill in the art would have a reasonable expectation of success at making a delivery mixture comprising a dendrimer and a nucleic acid capable of mediating RNAi given that antisense oligonucleotides and nucleic acids capable of mediating RNAi are both nucleic acids that encounter the same delivery problems. Further, Kang et al. teach both antisense oligonucleotides and siRNA formed strong complexes with dendrimers and both showed similar cellular distribution when delivered to the cells and finally Kang et al. has shown the siRNA delivered using dendrimers were capable of mediating RNAi, as required by the instant invention (see Kang et al., Discussion)

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER
AU 1635